Remarks

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 1-7, 9-10, 12-13, and 82-84 are pending in this application, with claim 1 being the independent claim.

Claims 1, 4-5 and 83-84 have been amended without prejudice or disclaimer. Support for the amendment may be found in the original claims, and in the specification, for example, in paragraphs [0019]-[0020], [0029]-[0030], [0104], [0137]-[0138], [0140] and [0143].

It is believed that these changes introduce no new matter, and their entry is respectfully requested.

Applicants reserve the right to pursue the amended subject matter in one or more continuation or divisional applications.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and further request that they be withdrawn.

Request for Examiner Interview Prior to Next Office Action

This Amendment and Reply is being filed with a Request for Continued Examination. Applicants respectfully request an interview after the Examiner has considered this paper and prior to the issuance of a new Office Action.

Request for Copies of References Cited by Examiner

The Examiner has cited non-patent literature references in support of the current rejections, but has not provided copies. Applicants respectfully request that the Examiner supply copies of these references (Lee *at al.* and Martinez-Picado *et al.*) if relied upon in a future Office Action. MPEP § 707.05(a).

Rejections Under 35 U.S.C. § 112, Written Description

The rejection of claims 1-10, 12, 13, and 82-84 for allegedly failing to comply with the written description requirement was maintained. Paper 20070405, p. 3. The Examiner alleges that the claims encompass the use of compounds such as siRNA, aptamers, ribozymes, antibodies, small molecule compounds, peptidomimetics, and homologs of Gag-binding proteins. Paper 20070405, p. 4. Applicants respectfully traverse this rejection for the reasons set forth in Applicants' previous response. Applicants provide the following additional remarks.

Applicants first note that claims 12-13 recite particular compounds, and therefore never encompassed the use of the broad range of unrelated compounds listed in the outstanding Office Action.

Second, Applicants note that while paragraph [0081] (page 28) to paragraph [0093] (page 32) disclose several dozen small molecule inhibitors, no siRNA, aptamers, ribozymes, antibodies, peptidomimetics, or homologs of Gag-binding proteins are disclosed. Therefore, to construe the claims as encompassing these molecules is not reasonable in view of the specification. MPEP § 2111.

Third, Applicants have amended claim 1 to recite a method comprising "orally" administering a maturation inhibitor. None of siRNA, aptamers, ribozymes, antibodies, peptidomimetics, and homologs of Gag-binding proteins can be administered orally in a method of treatment because they would be destroyed by stomach acid, digestive enzymes, and intestinal bacteria. The remaining claims depend from claim 1. Therefore, none of the claims encompasses the use of siRNA, aptamers, ribozymes, antibodies, peptidomimetics, and homologs of Gag-binding proteins.

As discussed in the Amendment and Reply filed January 22, 2007, the specification describes a number of maturation inhibitors. These maturation inhibitors fall within the scope of the compound recited in claim 1. For example, the specification describes betulin derivatives and dihydrobetulin derivatives that function as maturation inhibitors. *See,* e.g., Specification, ¶ [0084]. The specification also describes oleanolic acid derivatives, promolic acid derivatives, urosolic acid derivatives and platanic acid derivatives that function as maturation inhibitors. *Id.* These are examples of maturation inhibitors that may be administered orally, as recited in claim 1. Thus, the specification describes examples of the maturation inhibiting compounds of claim 1, and these examples are representative of the recited genus.

The amended claims are therefore fully supported by the written description. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection.

efficacy." Paper 20070405, p. 5. However, *Ex parte Balzarini* involved the rejection of claims in an application that was filed in 1987, *16 years before* the earliest filing date of the present application. Moreover, the art relied on by the Examiner in that case also dated from about 16 years prior to the earliest filing date of the present application. As stated in the MPEP,

> [t]he state of the art for a given technology is not static in time. . . . Therefore, the state of the prior art must be evaluated for each application based on its filing date.

MPEP § 2164.05(a).

In fact, subsequent to the decision in *Balzarini*, the Board of Patent Appeals and Interferences ("Board") refused to uphold an Examiner's rejection of claims directed to anti-viral compounds and methods of using such compounds, which encompassed treatment of HIV infection. *Ex parte Bodian*, 1995 WL 1696869 (Bd.Pat.App. & Interf.) (unpublished) (copy enclosed as **Exhibit A**) (slip opinion available at http://des.uspto.gov/Foia/ReterivePdf?flNm=fd951364.pdf). Since the Examiner's enablement rejection in the present case is broadly based on an alleged lack of predictability of extrapolating from *in vitro* to *in vivo* clinical results, the Board's discussion of the basis for the lack of utility rejection in *Bodian* is directly applicable to the present enablement rejection.

The application involved in the *Bodian* decision was filed in 1992. As the Board stated,

> The Balzarini opinion itself cannot serve as relevant evidence as to how the asserted utility would be judged by

> those working in the art when the application was filed in 1992. At best, *Balzarini* indicates what those skilled in the art would have believed *in 1987* as to predictability from *in vitro* tests. However, *Balzarini* does not create a *per se* rule of lack of utility for all AIDS-related inventions.

Ex parte Bodian, 1995 WL at *4. Moreover, the Board stated that the Examiner had failed to establish a *prima facie* case for lack of utility because the Examiner had failed to provide evidence that was *relevant to the filing date* of the application. *Id.*

Similar to the situation in *Bodian*, a review of the present record reveals a striking attempt on the part of the Examiner to shift the burden to Applicant to prove that the invention *is enabled*, rather than presenting relevant, specific evidence or reasoning to show that the invention is *not enabled* as required under the law. For example, in the Office Action mailed September 21, 2006, the Examiner explained the basis for the enablement rejection as follows: "[a]t the time the invention was made, successful implementation of HIV/AIDS therapy with a Gag p25 inhibitor was not routinely obtainable by those skilled in the art." Office Action, Sept. 21, 2006, p. 7. This sentiment was reiterated in the Office Action mailed April 18, 2007, in which the Examiner stated that "[t]he present specification does not describe any therapeutic property such as the binding specificity, selectivity and affinity, oral bioavailability, plasma concentration, cellular uptake, toxicity, lethal dose, or side effects." Paper 20070405, p. 8. It is clear from these passages that the Examiner is requiring Applicant to prove enablement of the invention before the Examiner has provided any evidence to suggest non-enablement.

The improper burden shifting in the context of this rejection is especially evident from the language used in the Office Action mailed September 21, 2006:

> The amount of direction is limited to a cell culture assay to determine the inhibitory effect of DSB on HIV maturation. There is no evidence that shows any correlation with *in vivo* efficacy. . . .
>
> The state of the art of development of pharmaceutical HIV inhibitors is highly unpredictable, since HIV replicates rapidly with a high mutational frequency and creates diverse 'quasi-species', which are favored by the Darwinian selective pressures.

Office Action, Sept. 21, 2006, pp. 7-8 (citations omitted). The so-called "state of the art" cited at page 8 of the September 21, 2006 Office Action in no way suggests that the claimed methods would *not* be able to treat HIV-1 infection in patients. The Examiner did not even allege that the cited art would not be able to treat HIV-1 infection; rather, the Examiner simply asserted that the cited art discusses "the complexity of extrapolating from *in vitro* to *in vivo* test results" and has to address "many factors such as serum half-life, bioavailability, clearance of the drugs themselves, cellular uptake, transport, metabolic activation, cell-, tissue-, and organ-specific toxicity." *Id.*, p. 8. In other words, according to the Examiner, the cited art does not provide a definitive demonstration that the methods *are* enabled. An enablement rejection cannot be maintained on the ground that the prior art fails to demonstrate that the invention *would work* when there is no evidence of record to suggest that the invention *would not work*.

Rejections Under 35 U.S.C. 112, First Paragraph, Enablement

The rejection of claims 1-10, 12, 13, and 82-84 for allegedly failing to comply with the enablement requirement was maintained. Applicants respectfully traverse this rejection for the reasons set forth in Applicants' previous response. Applicants provide the following additional remarks.

I. A Prima Facie Case of Lack of Enablement Has Not Been Established

The Examiner is respectfully reminded that, in order to make a rejection for lack of enablement, the Examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. *See* MPEP § 2164.04, citing *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). To satisfy this burden, the Examiner must provide "acceptable evidence or reasoning" to support an assertion of lack of enablement. *See In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971). Here, the Examiner has not provided relevant, specific evidence or sound scientific reasoning to suggest that the practice of the currently claimed methods would not have enabled a person of ordinary skill to treat HIV-1 infection in a patient. Indeed, the evidence of record weighs heavily in favor of adequate enablement for the claimed methods. Without presenting any relevant, specific evidence to back up the assertion of lack of enablement, the rejection cannot properly be maintained.

The Examiner cited *Ex parte Balzarini*, 21 USPQ2d 1892 (Bd. Pat. App. & Interfer. 1991) (non-precedential), for the proposition that "[*i*]*n vitro* testing is, at most, [a] useful tool for screening potential anti-viral agents but is not predictive of *in vivo*

Moreover, even assuming that the references cited by the Examiner demonstrated that the present invention would not work, these references are not relevant to the time period of the present claims and therefore do not support a *prima facie* case of nonenablement. The Examiner cited Martinez-Picado, *et al.*, *AIDS Clin. Care 10*:81-88 (1998) and Gait and Karn, *Trends Biotechnol. 13*:430-38 (1995). However, Martinez-Picado *et al.* and Gait and Karn were published in 1995 and 1998 -- about five and eight years prior to the 2003 earliest filing date for the present application -- and thus predate the relevant time period.

The Examiner also cited Lee, *et al.*, *Biochem. 42*:14711-19 (2003) in support of the rejection. However, Lee *et al.* refers to the toxicity of nucleoside analogues for mitochondrial DNA polymerase, which is a mechanism of toxicity that is not relevant to the compounds recited in the present claims because the recited compounds do not target viral reverse transcriptase. Therefore, Lee *at al.* is not relevant to establishing that the presently claimed method would cause toxic side effects.

Moreover, the question of whether the recited compounds may or may not be toxic is far outside the scope of a proper enablement inquiry. The present claims do not reference toxicity. Even if toxic reactions related to the claimed methods did occur, which has never been reported after dosing several hundred volunteers in clinical trials, they would merely be a *side effect* of the claimed method. But whether or not the method causes side effects is an issue for the FDA, not the PTO, and it has no relevance to the question of whether a person of ordinary skill in the art could have practiced the currently claimed methods without undue experimentation. *See, e.g., In re Anthony*, 414 F.2d 1383, 1395, 162 U.S.P.Q. 594, 604 (CCPA 1969) ("Congress has given the

responsibility to the FDA, not to the [PTO], to determine . . . whether drugs are sufficiently safe") (citation omitted). Applicants further note that all of the FDA-approved HIV therapies may cause side effects, and to require *no* side effects for the presently claimed method would be to require more than is required for FDA approval. *See* AIDSinfo, "Side Effects of Anti-HIV Medications," U.S. Dept. Health and Human Services (Reviewed Oct. 2005) at p. 2 (copy enclosed **as Exhibit B**).

II. The Evidence of Record Overwhelmingly Supports Enablement

The fact that no relevant, specific evidence or clear scientific reasoning has been presented to cast doubt on the enablement provided for the presently claimed invention is reason enough to require withdrawal of the enablement rejection. Applicants nonetheless submit that the evidence of record strongly supports the enablement of the claimed method. Of particular note in this regard is the data in the specification concerning DSB inhibition of HIV-1 and DSB toxicity. As the specification discloses, DSB is an example of compound of claim 1. The specification states:

> A robust virus inhibition assay was used to evaluate the anti-viral activity of DSB against primary HIV-1 isolates propagated in PMBC. . . . On day 7 post-infection, culture supernatant was removed from each well for p24 detection of virus replication and 50% inhibitory concentrations (IC_{50}) were calculated by standard methods.
>
> Table 3 shows the potent anti-viral activity of DSB against a panel of primary HIV-1 isolates. DSB exhibits

levels of activity similar to approved drugs that were tested in parallel. Importantly, the activity of DSB was not restricted by co-receptor usage.

Table 3

----------**IC_{50} (nM)**----------

Virus Isolate #	Co-Receptor usage	DSB	AZT	Nevirapine
BZ167	X4	4.0	2.2	31.2
92HT599	X4	9.8	5.8	25.3
US1	R5	5.6	0.9	22.1
19101N*	R5	3.8	2.4	59.4
3401N*	R5/X4	12.0	17.5	32.1
92US723	R5/X4	4.6	1.2	26.8
22101N*	R5/X4	2.6	0.9	4.9
Mean		**6.1**	**4.4**	**28.8**

Specification, Ex. 1, pp. 50-51. In addition, the specification, in Example 2, states:

The activity of DSB was tested against a panel of HIV-1 isolates resistant to approved drugs. These viruses were obtained from the NIH AIDS Research and Reference Reagent Program. . . . On day 5 post-infection, virus-induced cell killing was determined by the XTT method and the inhibitory activity of the compound was determined.

Table 4 shows the potent anti-viral activity of DSB against a panel of drug-resistant HIV-1 isolates. The results were not significantly different from those obtained

with the panel of wild-type isolates (Table 3), demonstrating that DSB retains its activity against virus strains resistant to all of the major classes of approved drugs.

Table 4

---------- IC_{50}(nM) ----------

Virus Isolate #	Mutation(s)	Co-Receptor usage	DSB	AZT	Nevirapine	Indinavir
NRTI-resistant						
1	K70R T215Y/F	R5/X4	4.4	86.4 (54X)*	ND	9.8
2	K70R T215Y/F	R5/X4	4.2	63.4 (40X)	ND	6.1
NNRTI-resistant						
3	Y181C	X4	1.0	5.1	>3800 (>177X)	2.5
4	K103N Y181C	X4	1.3	2.0	2630 (122X)	4.5
Protease-resistant						
5	V82A	X4	5.6	13.1	ND	39.7 (12X)
6	I84V	X4	5.5	14.4	ND	32.7 (10X)
7	L10R/M46I/ L63P/V82T/I 84V	X4	12.9	3.5	ND	72.5 (23X)

Id., Ex. 2, pp. 52-53. In addition, the specification discloses data on DSB toxicity in Example 1, as follows:

Toxicity of DSB was analyzed by incubating with PHA-stimulated PBMC for 7 days at a range of concentrations, then determining cell viability using the XTT method. The 50% cytotoxic concentration was >30

> μM, corresponding to an *in vitro* therapeutic index of approximately 5000.

Id., Ex. 1, p. 51. Therefore, the specification provides *in vitro* data on DSB's anti-HIV activity and its toxicity. References cited in the specification disclose additional *in vitro* data on the anti-HIV activity of other molecules that fall within the scope of the recited compounds. *Id.*, e.g., ¶ [0084].

In addition, as discussed in the Amendment and Reply filed January 22, 2007, the specification also discloses detailed information on the novel mechanism through which DSB and the other recited maturation inhibitors exert their anti-HIV activity. Examples 3-8 of the specification describe experimental data that show that maturation inhibitors target the SP1 cleavage site of the HIV-1 Gag protein. This mechanism of action makes it less likely that maturation inhibitors will be toxic in humans because they target a viral substrate rather than a cellular target; additionally, maturation inhibitors target a viral substrate rather then an enzymatic target.

The fact that this mechanism of action is novel with respect to HIV-1 therapies existing at the time of the invention also has important clinical implications because it means that the compounds recited in claim 1 will have activity against HIV-1 that is resistant to other classes of HIV-1 inhibitors. For example, protease-inhibitor resistant HIV-1 is sensitive to the maturation inhibitors of the present invention because: (i) while protease inhibitors target the protease enzyme, the maturation inhibitors of the present invention target the enzyme's substrate; (ii) mutations conferring resistance to protease inhibitors occur in structurally distinct regions of the HIV genome relative to mutations conferring resistance to maturation inhibitors; and (iii) protease inhibitor resistant

mutants do not exhibit cross-resistance to maturation inhibitors. In fact, recent data suggest that "HIV resistant to Protease Inhibitors (PI) may have *reduced* potential for the development of resistance to the HIV maturation inhibitor bevirimat." Panacos Press Release (May 29, 2007) (emphasis added) (copy enclosed **as Exhibit C**). Bevirimat, the subject of the May 29, 2007 press release, falls within the scope of the recited maturation inhibitors of claim 1. Therefore, because the claims require that the recited compounds possess the ability to suppress HIV-1 replication by inhibiting CA-SP1 cleavage, the detailed information in the specification concerning this mechanism of HIV inhibition by maturation inhibitors supports the enablement of the full scope of the claims.

Additional evidence of the enablement of the present invention is the fact that two maturation inhibitors within the scope of compounds recited in claim 1 have entered human clinical trials. These examples are bevirimat (aka DSB) and PA-040. *See* Panacos Press Release (March 12, 2007) (copy enclosed **as Exhibit D**); and Panacos Press Release (Feb. 27, 2007) (copy enclosed **as Exhibit E**). Moreover, bevirimat has shown significant antiviral activity in these trials. *Id.*; *see also* Panacos Press Release (June 20, 2007) (copy enclosed **as Exhibit F**). The specification teaches the dosage form (liquid), the administration route (oral) and the strength (250 mg per patient, or approximately 3.33 mg/kg) of bevirimat (aka DSB) that showed potent antiviral activity. *See*, specification, ¶¶ [0135]-[0136] and [0143]; and June 20, 2007 Press Release.

III. Summary

The Examiner has not presented any relevant, specific evidence or sound scientific reasoning to suggest that the claimed method would not be effective. Thus, the

Examiner has not met her initial burden of establishing a *prima facie* case of lack of enablement. For this reason alone, the rejection should be withdrawn. In addition, the evidence of record -- including data in the specification and the fact that the FDA has approved two maturation inhibitors for entry into clinical trials -- overwhelmingly suggests that the currently claimed method *would* be effective. Thus, Applicants respectfully request that the rejection be reconsidered and withdrawn.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Applicants respectfully request an interview with the Examiner once she has had the opportunity to consider the present amendment and response.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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1995 WL 1696869 (Bd.Pat.App. & Interf.)
(Cite as: 1995 WL 1696869 (Bd.Pat.App. & Interf.))

*1 THIS OPINION WAS NOT WRITTEN FOR PUBLICATION

Board of Patent Appeals and Interferences

Patent and Trademark Office (P.T.O.)
EX PARTE DALE L. BODIAN, JUDITH M. WHITE, IRWIN D. KUNTZ, JAY F. STEARNS AND R. BRYAN YAMASAKI
Appeal No. 95-1364
Application 07/919,287 [FN1]

NO DATE REFERENCE AVAILABLE FOR THIS DOCUMENT

David Larwood

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Before JOHN D. SMITH, SCHAFER and OWENS

Administrative Patent Judges.

SCHAFER

Administrative Patent Judge.

ON BRIEF

DECISION ON APPEAL

Applicants appeal the final rejection claims 1-6, 8-9, 12-17, and 23-36. We have jurisdiction pursuant to 35 U.S.C. § 134.

Background

The subject matter of the invention is a medical method. In particular, the claims are directed to a method for treating a viral condition caused by an enveloped virus. According to the specification

[e]nveloped viruses include a fusion protein that changes conformation from a native form to a fusogenic form. This promotes fusion of the viral membrane with the host cell membrane, resulting in injection of viral contents into the host cell. Specification, p. 1, lines 19-22. Applicants list the following families of viruses as enveloped viruses:

Togaviridae, Flaviviridae, Coronaviridae, Rhabdoviridae, Filoviridae, Paramyxoviridae, Orthmyxoviridae, Bunyaviridae, Arenaviridae, Retroviridae, Hepadnaviridae, Herpesviridae, Poxviridae and Iridoviridae.

Specification, p. 4, lines 31 - 34. The conditions which can be treated using the invention are said to include

rubella, yellow fever, rabies, influenza, Korean hemorrhagic fever, common colds, respiratory syncytial virus, measles, mumps, HIV, hepatitis B, Herpes simplex, CMV, chicken pox, smallpox, Marburg virus, hemorrhagic fever, Lassa fever and African swine fever.

Specification, p. 4, line 34 - p. 5, line 4.

According to applicants the viral condition is treated by administering a therapeutically effective amount of a substituted benzene compound to the patient. The substituted benzene compound is generically defined as a benzene compound comprising a 2-R1, 3-R2-1-OX1, 4-OX2 where at least one of R1 and R2 include a carbon linkage to the benzene ring and OX1 and OX2 are simultaneously hydroxy. See Claim 1. Applicants specification also tells us that the treatment is effective because the compound inhibits fusion of the viral membrane with the cell's endosomal membrane by binding near the stem region or the hinge region of the virus hemagglutinin glycoprotein. The bound compound reduces the ability of the fusion protein to adopt the fusogenic conformation. Specification, p. 1, line 31 - page 4, line 19.

Independent claims 1, 14, 23 and 26 are representative (Appendix of claims, p. 1-3):

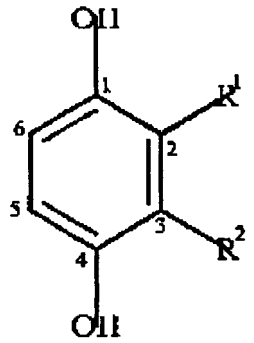
1. A method of treating a viral condition caused by an enveloped virus, said method comprising using a therapeutically effective amount of a compound selected from the group consisting of a substituted benzene, wherein said benzene comprises a 2-R1, 3-R2-1-OX1, 4-OX2 compound where at least one of R1 and R2 include a carbon linkage to the benzene ring and OX1 and OX2 are simultaneously hydroxy.

***2** 14. A method of treating a viral condition caused by an enveloped virus, said method comprising using a therapeutically effective amount of a compound having an IC_{50} of less than 10-3 M in the INF assay, wherein said compound comprises a substituted benzene, wherein said benzene comprises a 2- R1, 3-R2-1-OX1, 4-OX2 compound where at least one of R1 and R2 include a carbon linkage to the benzene ring and OX1 and OX2 are simultaneously hydroxy.

23. A method of treating a viral condition caused by an enveloped virus, said method comprising using a therapeutically effective amount of a compound which binds near the hinge region or near the stem region of hemagglutinin.

26. A method of treating a viral condition wherein the viral condition is caused by a virus having a fusion protein which has a native, non-fusogenic conformation and a second, fusogenic conformation, the method comprising using a therapeutically effective amount of a compound which binds to the fusion protein in the native conformation and reduces the ability of the fusion protein to adopt the fusogenic conformation.

As we understand the subject matter of claims 1 and 14, the substituted benzene compound set forth in these claim is represented by the following structural formula:



In other words, claims 1 and 14 as we understand them, require that 2-R1, 3-R2-1-OX1, and 4-OX2 substituents must all to be present on the benzene ring simultaneously. We have indicated the ring positions (1-6) according to standard benzene ring nomenclature. 1-OX1 and 4-OX2 have been indicated as hydroxy (OH) since claims 1 and 14 each require that "OX1 and OX2 are simultaneously hydroxy."

Applicants further define R1 and R2 at page 11 of their specification:

More generally, R1 and R2 each can be a hydrocarbon, saturated or unsaturated, potentially aromatic, generally hydrophobic, up to about C_{10} , but R1 and R2 taken together should include at least two carbon atoms. R1 or R2 or both can be electron donating or slightly electron withdrawing, e.g. - CH_2-O-CH_3, CH_2O-R3 (where R3 is a generally hydrophobic hydrocarbon, saturated or unsaturated, potentially aromatic, up to about C_{10}) or -CH2- COOH or esters thereof. R1 and R2 cannot both be strongly electron withdrawing, e.g. halogen or nitrile. R1 and R2 are preferably hydrophobic. R 1 and R2 can be part of a carbocyclic structure, e.g. naphthoquinone or compound 83, but should not be part of a highly polar heterocycle. Such a carbocyclic structure may be saturated, unsaturated, or aromatic. Preferably R1, and R2 if present, should have a carbon residue in the position . - to the 1,4-dihydroquinone ring.

We also note that claims 23 and 26 define the invention in terms of a step (e.g., "using a therapeutically effective amount of a compound" coupled with a function (e.g., which binds near the hinge region or near the stem region of hemagglutinin.

*3 The examiner asserts several grounds of rejection:

1. The subject matter of claims 1, 5-6, 8-9, 14-16, 26-27 and 31-36 is rejected under 35 U.S.C. § 101 as failing to be a useful process;

2. The subject matter of claims 23-25 is rejected under 35 U.S.C. § 101 as failing to be a useful process;

3. The subject matter of claims 13-15 and 23-30 is rejected under 35 U.S.C. § 112, 1, as failing to be supported by an enabling disclosure;

4. The subject matter of claims 1, 5-9, 12-15, 21, 23-28 and 31-36 [FN2] is rejected under 35 U.S.C. § 112, 1, as including subject matter which is not supported by an enabling disclosure;

5. The subject matter of claims 1-6, 8-9, 13-17, 21, 30, and 31-36 is rejected under 35 U.S.C. § 102(b) as anticipated by either of the following references:

Chemical Abstract 73:129328z Bogdanova et al. (Bogdanova) 1970

Chemical Abstract 85:56546e Grinev et al. (Grinev) 1976

6. The subject matter of claims 1-6, 8-9, 12-17 and 23-26 is rejected under 35 U.S.C. § 103 as unpatentable over the combination of Bogdanova and Grinev and the following references: [FN3]

Chemical Abstract 84:160055j	Thiel et al. (Thiel)	1976
US Patent 4,898,891	Lavie et al. (Lavie)	February 6, 1990
Soviet Union Inventor's Certificate 923,028	Ordzhokikidze Chem-Pharm (Ordzhokikidze)	February 23, 1983
Chemical Abstract 96:199209k	Korsakova et al. (Korsakova)	1982
Chemical Abstract 115:231795	Lyubchanskaya et al. (Lyubchanskaya)	1991

Disposition

We reverse the rejections based on 35 U.S.C. §§ 101 and 112; vacate the rejections under 35 U.S.C. § 102(b) and 103 and remand the application for further examination on these grounds; and enter a new ground of rejection under 35 U.S.C. § 12, 2.

Analysis

The Burden of proof

In proceedings before the PTO the examiner has the burden of establishing the prima facie case of unpatentability. In re Oetiker, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992); In re Fritch, 972 F.2d 1260, 1265, 23 USPQ2d 1780, 1783 (Fed. Cir. 1992); In re Piasecki, 745 F.2d 1468, 1472, 223 USPQ 785, 788 (Fed. Cir. 1984); In re Rinehart, 531 F.2d 1048, 1052, 189 USPQ 143, 147 (CCPA 1976). To meet this burden the examiner must present a factual basis supporting the conclusion that a prima facie case exists. See In re Freed, 425 F.2d 785, 787, 165 USPQ 570, 571 (CCPA 1970); In re Warner, 379 F.2d 1011, 1016, 154 USPQ 173, 177 (CCPA 1967); In re Lunsford, 357 F.2d 385, 391, 148 USPQ 721, 725 (CCPA 1966).

The rejections under 35 U.S.C. § 101

***4** With respect to the so called utility requirement of 35 U.S.C. § 101, the CCPA has described the requirements for establishing a prima facie case of lack of utility:

As a matter of Patent Office practice, a specification which contains a disclosure of utility which corresponds in scope to the subject matter sought to be patented must be taken as sufficient to satisfy the utility requirement of 101 for the entire claimed subject matter unless there is reason for one skilled in the art to question the objective truth of the statement of utility or its scope. Assuming that sufficient reason to question the statement of utility and its scope does exist, a

rejection for lack of utility under 101 will be proper on that basis; such a rejection can be overcome by suitable proofs indicating that the statement of utility and its scope as found in the specification are true. [Emphasis added.]
In re Langer, 503 F.2d 1380, 1391-92, 183 USPQ 288, 297 (CCPA 1974).

Rejection of claims 1, 5-6, 8-9, 14-16, 26-27 and 31-36

There is no assertion raised that the utility disclosed in the specification fails to correspond to the scope of the claimed subject matter. Indeed, the specification expressly states the utility as "treating a viral condition caused by an enveloped virus." Specification, p. 4, lines 21-22. This is the same utility as set forth in the claims. Thus, the stated utility must be considered sufficient unless the examiner presents evidence and reasoning which would give one having ordinary skill in the art reason to doubt the objective truth of the application's statement of utility.

The examiner correctly notes that many of the claims read on treating AIDS. The examiner asserts that [t]reatment efforts, and efforts to cure this group of related symptoms have produced no identifiable positive results. Examiner's answer, p. 3. However, the examiner has not provided any evidence which supports this assertion. The examiner's reliance on Ex parte Balzarini, 21 USPQ2d 1892 (Bd. Pat. App. & Interferences 1991), a non-precedential opinion of this board, does not help the examiner's position. In Balzarini the examiner provided ample evidence to support the position that those skilled in the art would not believe that successful in vitro testing would be a reasonable basis for predicting in vivo efficacy. This evidence included publications which were contemporaneous with and subsequent to Balzarini's 1987 filing date. Here the examiner has not provided any evidence to support the asserted lack of utility. The Balzarini opinion itself cannot serve as relevant evidence as to how the asserted utility would be judged by those working in the art when the application was filed in 1992. At best, Balzarini indicates what those skilled art would have believed in 1987 as to predictability from in vitro tests. However, Balzarini does not create a per se rule of lack of utility for all AIDS-related inventions. In making a rejection for lack of utility it is the examiner's burden to provide evidence showing that those working in the art would not believe the objective truth of the stated utility at the time the application was filed. Langer, 503 F.2d at 1391-92, 183 USPQ at 297. Such evidence is lacking here and the examiner has failed to make out a prima facie case for lack of utility.

***5** Because we hold that the examiner has not made out a prima facie case, it is not necessary for us to address the White declaration with respect to this ground of rejection.

The rejection of claims 1, 5-6, 8-9, 14-16, 26-27 and 31-36 under 35 U.S.C. § 101 is reversed. [FN4]

Rejection of claims 23-25

The examiner rejects these claims on a different theory. In the examiner's view the claims read on effecting various biochemical pathways and as such do not set

forth a viable utility. Examiner's Answer, p. 5. The examiner asserts that

> [u]nless the pathway at issue is critical to treating some condition, and the pathway modification and disease treatment are inexorably linked, such pathway modification is devoid [of] utility.... The skilled artisan could affect a biochemical pathway, in a patient without producing any therapeutic benefit or physiologically detectable effect.

Examiner's Answer, p. 6.

We do not agree with the examiner's implicit position that claims which read on affecting biochemical pathways necessarily do not set forth a viable utility. We know of no such per se rule. It may be that, based on appropriate evidence, claims directed to effecting biochemical pathways can be held to lack utility. However, we do not have to make that determination in this appeal because the rejected claims set forth a utility not just a pathway. Claim 23 specifically states that the method is for treating a viral condition...using a therapeutically effective amount of a compound.... viral condition is defined in the specification as

> rubella, yellow fever, rabies, influenza, Korean hemorrhagic fever, common colds, respiratory syncytial virus, measles, mumps, HIV, hepatitis B, Herpes simplex, CMV, chicken pox, smallpox, Marburg virus, hemorrhagic fever, Lassa fever and African swine fever.

Specification, p. 4, line 34 - p. 5, line 4. The claim also requires the use of a "therapeutically effective amount" of the compound. This phrase requires that the compound have a beneficial effect on a viral condition such as influenza. The claim does not encompass affecting a biochemical pathway without producing a therapeutic benefit or physiologically detectable effect as asserted by the examiner.

Additionally, as with claims 1, 5-6, 8-9, 14-16, 26-27 and 31-36, the examiner has failed to support the holding of lack of utility with any evidence which would present doubts as to the objective truth of the statements of utility in the specification and claims.

The rejection of claims 23-25 under 35 U.S.C. § 101 is reversed.

The rejections under 35 U.S.C. § 112, 1

The standards for establishing a prima facie case of lack of enablement is similar to that for lack of utility:

> [A] specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of Section 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.

***6** Fiers v. Revel, 984 F.2d 1164, 1171-72, 25 USPQ2d 1601, 1607 (Fed. Cir. 1993) quoting In re Marzocchi, 439 F.2d 220, 223, 169 USPQ 367, 369 (CCPA 1971).

The specification, when filed, must enable one skilled in the particular art to use the invention without undue experimentation. In re Goodman, 11 F.3d 1046, 1050, 29 USPQ2d 2010, 2013 (Fed. Cir. 1993); In re Wands, 858 F.2d 731, 737, 8 USPQ2d

1400, 1404 (Fed. Cir. 1988). The specification must provide enablement as broadly as the invention is claimed. Goodman, 11 F.3d at 1050, 29 USPQ2d at 2013, In re Vaeck, 947 F.2d 488, 496, 20 USPQ2d 1438, 1444 (Fed. Cir. 1991)

The rejection of claims 13-15 and 23-30 under 35 U.S.C. § 112, 1

The examiner has objected to the specification under 35 U.S.C. § 112, 1, concluding that the specification does not enable one having ordinary skill in the art to make and use the claimed invention. Claims 13-15 and 23-30 were rejected under 35 U.S.C. § 112, 1, for the reason set forth in the objection to the specification.

The examiner has failed to demonstrate that the applicants disclosure does not contain a teaching of the manner and process of using the claimed invention in terms which correspond in scope to the terms used in describing the invention. Thus, the examiner has the burden of providing evidence or reasoning to establish a basis to challenge the objective truth of the statements in the specification. Fiers, 984 F.2d at 1172, 25 USPQ2d at 1607. In the examiner's view certain critical information is missing from the disclosure. The examiner notes:

Applicants claim a group of compounds that possess a specific utility, yet fail to set forth the test or the compounds that might fit the test criteria. Claims to preventing disease conditions are presented, yet Applicant fails to provide information that would enable the skilled artisan to identify individuals in need of such preventive treatment. The instant invention proposes treating viral etiological agents embodying "a fusion protein which has a native, non-fusogenic conformation and a second, fusogenic conformation", yet fails to fails to [sic] provide information that would enable the skilled artisan to identify the specific etiological agents treatable by the claimed antiviral method.

Examiner's Answer p. 6-7. However, the absence of information from the specification is not a basis, alone, for concluding that the specification in not enabling. The examiner must also establish that because of the missing information, one having ordinary skill in the art would not be able to make and use the claimed invention without undue experimentation. The examiner has not met that burden in this case. The examiner has not provided any evidence which would allow us to hold that undue experimentation would be necessary to practice the claimed invention. For all the record shows, the alleged missing information is within the level of ordinary skill in the art. Such information need not be disclosed in the specification. In re Buchner, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); Lindemannn Maschinenfabrik GMBH v. American Hoist & Derrick Co., 730 F.2d 1452, 1463, 221 USPQ 481, 489 (Fed. Cir. 1984). Indeed, the specification preferably omits, that which is well known in the art. Hybritech, Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), cert. denied, 480 U.S. 947 (1987); Lindemann, 730 F.2d at 1463, 221 USPQ at 489.

*7 The rejection of claims 13-15 and 23-30 is reversed.

The rejection of claims 1, 5-9, 12-15, 21, 23-28 and 31-36

The examiner rejects claims 1, 5-9, 12-15, 21, 23-28 and 31-36 under 35 U.S.C. § 112, 1, holding that the subject matter is broader than the enabling disclosure. The

examiner asserts that the subject matter of claims 1, 5-9, 12-15, 21, 23-28 and 31-33 are enabled only as to the specific viral etiologic agents named in the specification. The examiner also asserts that the subject matter of claims 1, 5-9, 12-15, 21, 23-28 and 31-36 is enabled only as to the specifically named antiviral compounds. Examiner's Answer, p. 7.

As we indicated above, the examiner has the burden of proof. The examiner must provide evidence or reasoning tending to show that the person of ordinary skill in the art could not practice the invention with unexemplified compounds and etiological agents within the scope of the claims without undue experimentation. The examiner has not met that burden. The examiner has presented no evidence or reasoning tending to show that undue experimentation would be necessary.

The examiner notes that the disclosure as filed does not include an OX compound as required by, for example, by claims 1 and 14. However, these claims expressly require OX1 and OX2 to be OH thus limiting these claims to hydroquinone derivatives. The examiner has not provided any evidence which establishes that the person having ordinary skill in the art would not be able to practice the claimed invention using hydroquinone derivatives without undue experimentation.

The rejection of claims 1, 5-9, 12-15, 21, 23-28 and 31-36 under 35 U.S.C. § 112, 1, is reversed.

The prior art rejections

The rejection of claims 1-6, 8-9, 13-17, 30, and 31-36 under 35 U.S.C. § 102(b) [FN5]

The examiner has rejected these claims over either of Grinev or Bogdanova, two Chemical Abstracts, abstracting Russian language articles by Grinev et al. and Bogdanova et al.

For a reference to be anticipatory, it must describe, either expressly or under the principles of inherencey, each and every feature of the claimed invention. Verdegaal Bros. v. Union Oil Co., 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir.), cert. denied, 484 U.S. 827 (1987); RCA Corp. v. Applied Digital Data Sys., Inc., 730 F.2d 1440, 1444, 221 USPQ 385, 388 (Fed. Cir. 1984). Neither abstract appears to expressly describe a compound falling within the scope of rejected claims 1-6, 8-9, 13-17, or 31-36, and the examiner has not provided an explanation of how the other limitations of the claims are met by the abstracts. The examiner has also not explained how the abstracts expressly describe a compound which binds to a fusion protein required by claim 30. No evidence showing or reasoning explaining how the claimed subject matter is inherently described by the abstracts has been provided. We recognize that the Bogdanova abstract refers to aryl and alkyl analogs of p-benzoquinone and hydroquinone halides. We find this teaching ambiguous and the examiner has not provided an explanation of how the aryl or alkyl analogs meet the claim limitations. Thus, neither Bogdanova and Grinev describe an embodiment within the scope of the claimed subject matter.

*8 While we are in effect reversing the examiner's rejection under 102(b) based on the Grinev and Bogdanova abstracts, we note that the Russian language publications which were abstracted appear to be highly pertinent to the claimed subject matter. These publications are not of record in the application. The examiner has not indicated that the references are not available in the PTO or that attempts to obtain the articles through inter-library loan were unsuccessful. We therefore, vacate the rejection and remand the application to the jurisdiction of the examiner for further prosecution and consideration of the Bogdanova and Grinev articles.

The rejection of claims 1-6, 8-9, 12-17 and 23-26 under 35 U.S.C. § 103

The examiner has rejected these claims under 35 U.S.C. § 103 as unpatentable over the combination of Leach et al., Grinev, Bogdanova, Thiel, Korsakova, Lyubchanskaya, Ordzhonikidze and Lavie. We vacate and remand this rejection also.

The examiner's answer relies on and discusses a Leach et al. reference. Examiner's Answer, p. 8. This reference, however, is not of record in the application, A copy of the reference is not present in the application file. Nor is it listed on the PTO Forms 852 and 1449 of record. Thus, we are unable to evaluate the teachings of the reference. In addition, the rejection relies on the meager descriptions of abstracts of foreign language publications. These publications appear highly relevant to the claimed subject matter. The publications appear to be available through interlibrary loan. The state of the current record precludes us from evaluating this rejection.

Accordingly, we vacate the rejection of claims 1-6, 8-9, 12-17 and 23-26 under 35 U.S.C. § 103 and remand the application for further proceedings including properly including a copy of the Leach et al. reference and consideration of the full text of the abstracted articles.

New Ground of Rejection under 35 U.S.C. § 112, 2

Claims 31-33 are rejected under 35 U.S.C. § 112, 2, as indefinite. These claims are dependant on claims 1, 14 and 27, respectively. As such they are subject to the mandatory claim construction of of 112, 4. That paragraph provides in part:

> A claim in dependent form shall be construed to incorporate by reference all limitations of the claim to which it refers.

Thus the limitation of claims 1, 14 and 27 must be read into claims 31-33. Each of claims 1, 14 and 27 requires that OX1 AND OX2 are simultaneously hydroxy. Claims 31-33 each include the limitation wherein one of OX1 AND OX2 is hydroxy and the other is OR4 where R4 is saturated or unsaturated hydrocarbon of less than four carbons. Thus, claims 31-33 are internally inconsistent in simultaneously requiring (1) that OX1 and OX2 both be hydroxy and (2) that only one of OX1 and OX2 be hydroxy and the other be OR4. The inconsistency renders the subject matter of the claims 31-33 indefinite.

*9 This decision contains a remand and a new ground of rejection pursuant to 37 CFR § 1.196(b) (amended effective Dec. 1, 1997, by final rule notice, 62 Fed. Reg. 53,131, 53,197 (Oct. 10, 1997), 1203 Off. Gaz. Pat. & Trademark Office 63, 122 (Oct. 21, 1997)). 37 CFR § 1.196(b) provides that, A new ground of rejection shall not be

considered final for purposes of judicial review. In addition 37 CFR § 1.196(e) provides that a decision which includes or allows a remand is not final for purposes of judicial review.

37 CFR § 1.196(b) also provides that the appellant, WITHIN TWO MONTHS FROM THE DATE OF THE DECISION, must exercise one of the following two options with respect to the new ground of rejection to avoid termination of proceedings (1.197(c)) as to the rejected claims:

(1) Submit an appropriate amendment of the claims so rejected or a showing of facts relating to the claims so rejected, or both, and have the matter reconsidered by the examiner, in which event the application will be remanded to the examiner....

(2) Request that the application be reheard under 1.197(b) by the Board of Patent Appeals and Interferences upon the same record....

No time period for taking any subsequent action in connection with this appeal may be extended under 37 CFR § 1.136(a).

REVERSED-IN-PART, VACATED-IN-PART, REMANDED, 1.196(b)

BOARD OF PATENT APPEALS AND INTERFERENCES

JOHN D. SMITH

Administrative Patent Judge

RICHARD E. SCHAFER

Administrative Patent Judge

TERRY J. OWENS

Administrative Patent Judge

FN1. Application for patent filed July 24, 1992.

FN2. This rejection was actually expressed by the examiner as two separate rejections. Claims 34-36 were subject to only one of the two rejections. Because of our disposition of the rejections we do not have to distinguish between the two grounds.

FN3. We note that the examiner's statement and discussion of the rejection refers to a Leach et al. reference. Examiner's Answer, p. 8. However, this reference is not listed on page 2 of the Answer setting out the prior art relied upon, a copy of the reference could not be located in the record, nor were we able to find it listed on the PTO Forms 892 and 1449 of record.

FN4. Our reversal of this rejection should not be construed as an indication that we are questioning the truth of the examiner's statement that "[t]reatment efforts, and efforts to cure this group of related symptoms have produced no identifiable positive results." The examiner may very well be right on this point. However, the examiner must provide evidence to prove this assertion.

FN5. The examiner's statement of the rejection also refers to claim 21. Examiner's Answer, p. 8. However, claim 21 has apparently been canceled.

1995 WL 1696869 (Bd.Pat.App. & Interf.)

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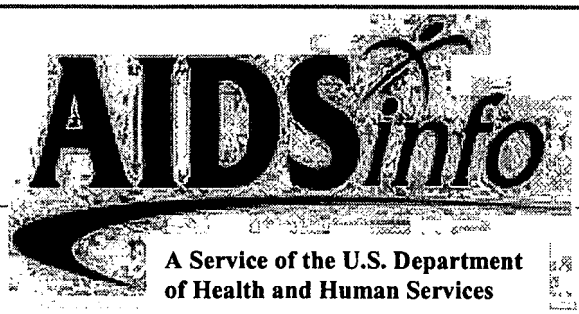

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Fact Sheets

Side Effects of Anti-HIV Medications

Health Information for Patients

October 2005

P.O. Box 6303, Rockville, MD 20849-6303
Telephone: 1-800-448-0440
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Fax: 301-519-6616
TTY/TTD: 888-480-3739
Live Help: http://aidsinfo.nih.gov/LiveHelp
E-mail: ContactUs@aidsinfo.nih.gov
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AIDSinfo

A Service of the U.S. Department of Health and Human Services

Side Effects of Anti-HIV Medications

Anti-HIV medications help people infected with HIV lead longer, healthier lives. The goal of HIV treatment is to reduce the amount of virus in a person's body and prevent destruction of the immune system.

Twenty-one anti-HIV medications have been approved by the U.S. Food and Drug Administration (FDA) for the treatment of HIV. These medications must be given in combination, and all of the drugs may cause negative side effects. Such side effects range from mild to life-threatening.

This series of fact sheets discusses some of the major side effects of anti-HIV medications. The information in this series is based on the U.S. Department of Health and Human Services' *Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents* (available at **http://aidsinfo.nih.gov/guidelines**) and *Management of Metabolic Complications Associated with Antiretroviral Therapy for HIV-1 Infection: Recommendations of an International AIDS Society-USA Panel* (available at **http://www.iasusa.org/pub/metcomp.html**).

Table of Contents

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Hepatotoxicity

What is hepatotoxicity?

Hepatotoxicity is a general term for liver damage. Medications, including those used to treat HIV infection, may cause hepatotoxicity. Hepatotoxicity has developed in HIV infected people taking anti-HIV medications from three classes: **nucleoside reverse transcriptase inhibitors (NRTIs)**, **non-nucleoside reverse transcriptase inhibitors (NNRTIs)**, and **protease inhibitors (PIs)**.

There are several specific conditions that all fall within the general category of hepatotoxicity. These conditions include:

- hepatitis—inflammation of the liver
- hepatic necrosis—death of liver cells
- hepatic steatosis—too much fat in the liver; may be associated with a life-threatening condition called *lactic acidosis* (see **Lactic Acidosis Fact Sheet**)

What are the symptoms of hepatotoxicity?

The first sign of damage to the liver is an increase in liver **enzyme** levels in the blood. When the liver is damaged, its enzymes are released into the bloodstream, where the levels can be measured by blood tests. These are called **liver function tests (LFTs)**. Enzyme levels that are routinely checked as part of LFTs include:

- alanine aminotransferase (ALT)
- aspartate aminotransferase (AST)
- gamma-glutamyltransferase (GGT)

The signs and symptoms of hepatotoxicity vary depending on how badly the liver is damaged. Symptoms of liver damage include:

- nausea
- vomiting
- abdominal pain
- loss of appetite
- diarrhea
- feeling tired or weak
- jaundice (yellowing of the skin and eyes)
- hepatomegaly (liver enlargement)

Terms Used in This Fact Sheet:

Enzyme: *a special protein that speeds up chemical reactions.*

Liver function tests (LFTs): *tests that measure the blood levels of liver enzymes (proteins made and used by the liver) to determine if your liver is working properly.*

Non-nucleoside reverse transcriptase inhibitor (NNRTI): *class of anti-HIV medication. NNRTIs work by blocking reverse transcriptase, a protein that HIV needs to make copies of itself. The NNRTIs approved by the FDA are Rescriptor, Sustiva, and Viramune.*

Nucleoside reverse transcriptase inhibitor (NRTI): *class of anti-HIV medication. NRTIs are faulty versions of the building blocks (nucleosides) used by reverse transcriptase, a protein that HIV needs to make copies of itself. The NRTIs approved by the FDA are Combivir, Emtriva, Epivir, Epzicom, Hivid, Retrovir, Trizivir, Truvada, Videx, Viread, Zerit, and Ziagen.*

Protease inhibitor (PI): *class of anti-HIV medication. PIs work by blocking protease, a protein that HIV needs to make copies of itself. The PIs approved by the FDA are Agenerase, Aptivus, Crixivan, Fortovase, Invirase, Kaletra, Lexiva, Norvir, Reyataz, and Viracept.*

Which anti-HIV medications cause hepatotoxicity?

All FDA-approved NRTIs, NNRTIs, and PIs are associated with hepatotoxicity.

NRTIs, especially Zerit (stavudine), Videx (didanosine), and Retrovir (zidovudine), are associated with lactic acidosis and hepatic steatosis.

NNRTIs, especially Viramune (nevirapine), are associated with hepatitis and hepatic necrosis. If you and your doctor decide to use Viramune in your HIV treatment regimen, you will likely be instructed to take only one pill a day for the first 14 days, then to increase

This information is based on the U.S. Department of Health and Human Services' *Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents* (available at **http://aidsinfo.nih.gov**).

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Hepatotoxicity (continued)

to two pills a day. This dosing schedule may decrease your risk of developing hepatotoxicity. Viramune-associated hepatotoxicity usually occurs within the first 12 weeks of taking the drug. Women appear to be at increased risk of liver damage. All patients starting therapy with Viramune should have LFTs every 2 weeks for the first month, then every month for the next 2 months, and then every 1 to 3 months throughout treatment.

PIs, especially full-dose Norvir (ritonavir) and Norvir-boosted Aptivus, are also associated with hepatotoxicity. Unlike Viramune, PIs may cause hepatotoxicity at any time. Patients infected with both HIV and hepatic C virus (HCV) may be at particular risk for developing hepatotoxicity while taking PIs.

Are there other risk factors for developing hepatotoxicity?

Yes. Other risk factors include:

- infection with hepatitis B or C virus
- high levels of certain liver enzymes prior to starting anti-HIV medications
- alcohol use
- use of other medications that damage the liver
- pregnancy

Can hepatotoxicity be prevented?

Because hepatotoxicity is poorly understood, it is not clear how it can be prevented. If you are worried about hepatotoxicity, one of the most important things you can do is to get checked for liver disease before starting anti-HIV medications. If you have liver disease or any risk factors for developing hepatotoxicity, you and your doctor may choose an HIV treatment regimen that minimizes the risk of liver damage. You should have LFTs performed frequently, especially when you first start your HIV treatment regimen.

What should I do if I develop hepatotoxicity?

Call your doctor if you develop any of the symptoms of hepatotoxicity. In some cases, hepatotoxicity goes away without changes in anti-HIV medications. Most cases, however, require that medications be stopped or changed. It is important that you do not stop or make any changes to your treatment regimen before talking with your doctor.

For more information:

Contact your doctor or an *AIDSinfo* Health Information Specialist at 1–800–448–0440 or **http://aidsinfo.nih.gov**.

This information is based on the U.S. Department of Health and Human Services' *Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents* (available at **http://aidsinfo.nih.gov**).

Reviewed October 2005

Hyperglycemia

What is glucose?

Glucose, commonly called blood sugar, is the body's main energy source. Your body breaks down the food you eat and converts it to glucose. Your cells take glucose from your blood and use it to make energy.

What is hyperglycemia?

Hyperglycemia occurs when you have a higher than usual level of glucose in your blood. This can happen shortly after you have eaten a big meal and is not a problem if your glucose level returns to normal.

Cells remove glucose from the blood in response to **insulin**. If your pancreas doesn't make enough insulin, glucose can't enter the cells and remains in the blood. Blood glucose levels can also get too high if cells are unable to respond to insulin properly (**insulin resistance**). Without glucose, your cells are unable to make energy and can't function properly.

Is hyperglycemia the same as diabetes?

Diabetes mellitus is a disease that occurs when the body can't use glucose properly. Hyperglycemia is a symptom of diabetes; however, you can have hyperglycemia without having diabetes.

What are the symptoms of hyperglycemia?

The most common symptoms of hyperglycemia are increased urination, excessive thirst or hunger, and unexplained weight loss.

What causes hyperglycemia and diabetes?

Treatment with HIV **protease inhibitors** (PIs) and infection with hepatitis C virus increase the risk of hyperglycemia and diabetes in people with HIV. The risk of developing hyperglycemia is about the same with all PIs.

People who are older, overweight, have family members with diabetes, or are from certain ethnic groups are also at greater risk for developing hyperglycemia.

Terms Used in This Fact Sheet:

Hypoglycemic medications: *medications used to decrease the level of glucose in the blood. Common oral hypoglycemic medications include Amaryl, Avandia, Glucophage, and Glucotrol.*

Insulin: *a hormone made by the pancreas. Insulin directs cells to take up glucose from the blood.*

Insulin resistance: *Insulin resistance occurs when cells are unable to respond to (resist) insulin's message to take up glucose from the blood.*

Protease inhibitor (PI): *class of anti-HIV medication. PIs work by blocking protease, a protein that HIV needs to make copies of itself. The PIs approved by the FDA are Agenerase, Aptivus, Crixivan, Fortovase, Invirase, Kaletra, Lexiva, Norvir, Reyataz, and Viracept.*

I am taking a PI and am worried about hyperglycemia. What should I do?

Tell your doctor if you have symptoms of hyperglycemia and discuss other risk factors you may have for hyperglycemia or diabetes. Do your best to maintain a healthy body weight.

A fasting blood glucose test measures the level of glucose in your blood and is used to diagnose hyperglycemia. You should have this test every 3 to 4 months during the first year you take a PI.

What happens if I develop hyperglycemia?

You and your doctor will discuss your treatment options. For most people, hyperglycemia goes away if they stop taking PIs. Don't stop taking any medication without first talking with your doctor. Together you may decide to make changes to your HIV treatment regimen.

You and your doctor may decide to continue using PIs in your treatment regimen despite your hyperglycemia. Your doctor may suggest you take **hypoglycemic medications** (by mouth) or insulin (injected under the skin) to decrease your blood glucose levels.

For more information:

Contact your doctor or an *AIDSinfo* Health Information Specialist at 1–800–448–0440 or **http://aidsinfo.nih.gov**.

This information is based on the U.S. Department of Health and Human Services' *Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents* (available at **http://aidsinfo.nih.gov**).

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Hyperlipidemia

What is hyperlipidemia?

Hyperlipidemia is an increase in the amount of fat (such as **cholesterol** and **triglycerides**) in the blood. These increases can lead to heart disease and **pancreatitis**.

Which anti-HIV medications can cause hyperlipidemia?

Some **protease inhibitors** (PIs) can raise blood lipid (fat) levels. Some PIs, such as Norvir, are more likely to cause hyperlipidemia than other PIs. Sustiva is a non-protease inhibitor drug that can also raise blood lipid levels.

Other factors can increase your risk of developing hyperlipidemia. Risks you can control include your alcohol intake, physical activity, and diet. Other risks include hypothyroidism, diabetes, and genetic factors. Oral contraceptives (birth control pills) can also increase triglycerides and total cholesterol.

What are the symptoms of hyperlipidemia?

Hyperlipidemia has no symptoms. The only way your doctor can diagnosis it is through laboratory tests. Your doctor should order a **lipid profile** when you start anti-HIV medication. Once your baseline lipid levels are determined, your doctor should monitor your levels every 3 to 4 months, or at least once a year.

What can I do if I have hyperlipidemia?

There are several things you can do to control your cholesterol and triglyceride levels. You can switch to a low-fat diet and control your weight. Your doctor may refer you to a dietician for help with your diet. Regular aerobic exercise has been shown to lower cholesterol. Quitting smoking and avoiding or limiting alcohol can also lower your cholesterol. Keeping your blood pressure under control is critical; you may need to take medication to lower your blood pressure.

What medications are used to treat hyperlipidemia?

You and your doctor may decide that you should take a cholesterol-lowering medication. This might be a medication from the statin group. Examples of statins are Lipitor (atorvastatin) and Pravachol (pravastatin). If statins are not effective, another medication from a group called fibrates might be added. Lopid (gemfibrozil) and Tricor (fenofibrate) are drugs from the fibrate group. All of these medications can cause serious side effects and should be taken only as directed by your doctor.

Terms Used in This Fact Sheet:

Cholesterol: *a waxy, fat-like substance present in every cell in your body. Your liver produces cholesterol from stored carbohydrates and fats. Certain foods provide additional amounts of cholesterol, which may be more than your body needs. Cholesterol levels that are too high increase your risk of heart disease.*

Lipid profile: *a group of tests that indicates your risk of heart disease. The lipid profile tests levels of total cholesterol, HDL-cholesterol (good cholesterol), LDL-cholesterol (bad cholesterol), and triglycerides.*

Pancreatitis: *inflammation of the pancreas that can produce severe pain and debilitating illness.*

Protease inhibitor (PI): *class of anti-HIV medication. PIs work by blocking protease, a protein that HIV needs to make copies of itself. The PIs approved by the FDA are Agenerase, Aptivus, Crixivan, Fortovase, Invirase, Kaletra, Lexiva, Norvir, Reyataz, and Viracept.*

Triglycerides: *a type of fat-like substance. Fats from food are digested and released as triglycerides into the bloodstream. Triglycerides help transfer energy from food into cells. However, triglyceride levels that are too high increase your risk of heart disease and have been associated with diabetes and pancreatitis.*

Will I need to change my HIV treatment regimen?

If your hyperlipidemia is severe or you do not respond to other treatments, you and your doctor may decide to change your anti-HIV medications. One option may be to replace your PI(s) with an anti-HIV medication from a different class; this might mean changing your entire regimen.

For more information:

Contact your doctor or an *AIDSinfo* Health Information Specialist at 1–800–448–0440 or **http://aidsinfo.nih.gov**.

This information is based on the U.S. Department of Health and Human Services' *Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents* (available at **http://aidsinfo.nih.gov**).

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Lactic Acidosis

What is lactic acidosis?

Lactic acidosis is a life-threatening condition caused by too much lactate in the blood and low blood pH. Low blood pH means that your blood contains too much acid, which can be harmful to the cells of your body.

What is lactic acid?

Lactic acid is a chemical byproduct of energy production in cells. Cells contain mitochondria, rod-like structures that serve as a cell's powerhouse. Mitochondria help convert the food you eat into the energy you need to function.

The food you eat is broken down into a type of sugar called glucose. Mitochondria use oxygen to turn glucose into energy. If there is not enough oxygen or if the mitochondria aren't working properly, cells must make energy by an alternative method. Making energy by this alternative method produces lactic acid as a byproduct.

Lactic acid is quickly converted to lactate in the blood. Though lactic acid and lactate are not the same, the terms are often used interchangeably. Lactate is formed when lactic acid loses a hydrogen atom. The hydrogen atom lost by lactic acid stays in the blood; this decreases the blood's pH and makes it more acidic.

Your muscles produce lactic acid and lactate when you exercise. It is the lactate in your muscles that makes them feel sore after a workout. Lactate is broken down by your liver, so if your body produces too much lactate, your liver may have a hard time keeping up.

What causes too much lactate?

High levels of lactate in the blood, referred to as *hyperlactatemia*, occur either when you make too much lactate or when your liver isn't working properly and can't break it down.

Terms Used in This Fact Sheet:

Liver function tests (LFTs): *tests that measure the blood levels of liver enzymes (proteins made and used by the liver) to determine if your liver is working properly.*

Mitochondrial toxicity: *also referred to as mitochondrial dysfunction. Damage to the mitochondria that can cause problems in the heart, nerves, muscles, pancreas, kidneys, and liver. It may also cause changes in the blood, such as thrombocytopenia (too few platelets), anemia (too few red blood cells), and neutropenia (too few neutrophils). Mitochondrial damage can lead to lactic acidosis and hepatic steatosis (fatty liver) and may also play a role in lipodystrophy* (see **Lipodystrophy Fact Sheet**).

Nucleoside reverse transcriptase inhibitor (NRTI): *class of anti-HIV medication. NRTIs are faulty versions of the building blocks (nucleosides) used by reverse transcriptase, a protein that HIV needs to make copies of itself. The NRTIs approved by the FDA are Combivir, Emtriva, Epivir, Epzicom, Hivid, Retrovir, Trizivir, Truvada, Videx, Viread, Zerit, and Ziagen.*

Nucleoside reverse transcriptase inhibitors (NRTIs) can cause hyperlactatemia by disrupting the function of the mitochondria. This is known as **mitochondrial toxicity**. When the mitochondria don't work efficiently, excess lactate is produced.

NRTIs can also cause the liver to become fatty, a condition called *hepatic steatosis* (see **Hepatotoxicity Fact Sheet**). A fatty liver doesn't work well and can't break down lactate efficiently.

Severe hyperlactatemia leads to lactic acidosis. Lactic acidosis is a serious but very rare complication of treatment with NRTIs. Although all NRTIs are associated with hyperlactatemia and lactic acidosis, people taking Zerit (stavudine) and Videx (didanosine) seem to be at greater risk than people taking other NRTIs.

This information is based on the U.S. Department of Health and Human Services' *Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents* (available at http://aidsinfo.nih.gov).

Reviewed October 2005

Lactic Acidosis (continued)

Are there other risk factors for lactic acidosis?

Yes. Women and people who are overweight are at increased risk of developing hepatic steatosis and lactic acidosis. Fatal lactic acidosis has also occurred in pregnant women taking a combination of Zerit and Videx. HIV infected patients taking Rebetol (ribavirin) for hepatitis C virus infection may also be at increased risk for lactic acidosis.

What are the symptoms of hyperlactatemia and lactic acidosis?

You can have mild hyperlactatemia without experiencing any symptoms.

Signs and symptoms of severe hyperlactatemia and lactic acidosis are:

- persistent nausea, vomiting, and abdominal pain
- unexplained tiredness
- shortness of breath
- rapid breathing
- enlarged or tender liver
- cold or blue hands and feet
- abnormal heart beat
- weight loss

What should I do if I experience these symptoms?

Tell your doctor right away if you have any of the symptoms of lactic acidosis. Your doctor may then order blood tests, including:

- **liver function tests (LFTs)**
- lactate level (this test is difficult to do and is not done routinely)
- electrolyte level
- blood pH level

Your doctor should also perform a physical exam to check for an enlarged liver and may also order a CT scan or ultrasound of your liver.

What does my lactate level mean?

Lactate levels are usually reported as mmol/dL (millimoles of lactate per deciliter of blood). Lactate levels of 2 to 5 mmol/dL are elevated and should be considered with any symptoms you have. Levels greater than 5 mmol/dL are abnormal, and levels greater than 10 mmol/dL indicate a serious and possibly life-threatening situation.

Lactate levels may vary depending on how the test was performed and which lab did the testing. Your doctor can help you understand what your lactate level means.

What is the treatment for lactic acidosis?

Lactic acidosis is treated by stopping any NRTIs you are taking. You may need to be hospitalized. Some people with lactic acidosis need intravenous (IV) fluids and a machine to help them breathe. Some doctors recommend giving riboflavin (vitamin B2), thiamine (vitamin B1), coenzyme Q, L-carnitine, or vitamins C, E, and K to patients with lactic acidosis, but the effectiveness of these treatments is uncertain.

You should not stop taking any anti-HIV medications without talking with your doctor, even if you have symptoms of lactic acidosis. If you are diagnosed with lactic acidosis, you and your doctor will decide how to stop your anti-HIV medications, when to restart medications, and which ones to take when you go back to treatment.

If you have only mild hyperlactatemia and no symptoms, you may not need to change your HIV treatment regimen. At this time, people with mild hyperlactatemia do not seem to be at increased risk for lactic acidosis.

For more information:

Contact your doctor or an *AIDSinfo* Health Information Specialist at 1–800–448–0440 or **http://aidsinfo.nih.gov**.

This information is based on the U.S. Department of Health and Human Services' *Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents* (available at http://aidsinfo.nih.gov).

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Lipodystrophy

What is lipodystrophy?

Lipodystrophy, also called fat redistribution, is a disturbance in the way your body produces, uses, and stores fat. There are two different kinds of lipodystrophy. In *fat wasting*, also known as *lipoatrophy*, fat is lost from particular areas of the body, especially the arms, legs, face, and buttocks. The second kind of lipodystrophy is *fat accumulation*, also known as *hyperadiposity*. In fat accumulation, fat builds up in particular parts of the body, especially the belly, breasts, and back of the neck.

What does lipodystrophy look like?

Places where fat may accumulate:

- back of the neck and upper shoulders (often described as "buffalo hump")
- abdomen (also called "protease paunch" or "Crixivan potbelly")
- breasts (in both men and women)
- lipomas (fatty growths in different parts of the body)

Places where fat may be lost:

- face (sunken cheeks, temples, and eyes)
- arms and legs (veins may become more visible; this is called "roping")
- buttocks

Terms Used in This Fact Sheet:

Baseline: *an initial measurement made before starting therapy and used as a reference point.*

Metabolic: *referring to the buildup or breakdown of the body's molecular building blocks. These building blocks provide the material and energy that your body needs to function.*

Magnetic resonance imaging (MRI): *a way to take pictures of the inside of the body. MRI uses magnetic fields and radio waves instead of x-rays. MRIs are particularly useful for taking pictures of the body's soft tissues and organs.*

Non-nucleoside reverse transcriptase inhibitor (NNRTI): *class of anti-HIV medication. NNRTIs work by blocking reverse transcriptase, a protein that HIV needs to make copies of itself. The NNRTIs approved by the FDA are Rescriptor, Sustiva, and Viramune.*

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Protease inhibitor (PI): *class of anti-HIV medication. PIs work by blocking protease, a protein that HIV needs to make copies of itself. The PIs approved by the FDA are Agenerase, Aptivus, Crixivan, Fortovase, Invirase, Kaletra, Lexiva, Norvir, Reyataz, and Viracept.*

Are there any other disorders that occur along with lipodystrophy?

If you have lipodystrophy, you may also have other **metabolic** disorders. These disorders include *hyperlipidemia* (see **Hyperlipidemia Fact Sheet**), *hyperglycemia* (see **Hyperglycemia Fact Sheet**) or, rarely, *lactic acidosis* (see **Lactic Acidosis Fact Sheet**). Lipodystrophy in combination with hyperlipidemia and insulin resistance is called *lipodystrophy syndrome.*

What causes lipodystrophy?

Early studies suggested that lipodystrophy was associated with the use of **protease inhibitors (PIs)**, a class of commonly prescribed anti-HIV drugs. However, other studies have shown that lipodystrophy also occurs in people who have never taken PIs. Evidence now suggests that lipodystrophy is linked to taking **nucleoside reverse transcriptase inhibitors (NRTIs)** and PIs at the same time.

This information is based on the U.S. Department of Health and Human Services' *Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents* (available at **http://aidsinfo.nih.gov**).

Reviewed October 2005

Lipodystrophy (continued)

Other risk factors for lipodystrophy include:

- age—older people are at higher risk for lipodystrophy
- race—whites are at higher risk for lipodystrophy
- sex—men are more likely to experience fat loss in their arms and legs, while women tend to have an increase in abdominal and breast fat
- length and severity of HIV infection—the longer you have been infected and the more severe your infection, the higher your risk for lipodystrophy
- a **baseline** body mass index (BMI) in the obese range or significant weight changes are risk factors for lipodystrophy
- baseline immune system health and how well your immune system recovered after starting anti-HIV medications are also factors

Which anti-HIV drugs are most likely to cause lipodystrophy?

Zerit (stavudine, d4T) is one NRTI that has been specifically shown to cause fat loss. PIs may increase the risk of fat accumulation. The longer you take NRTIs and PIs, the greater your chance of developing lipodystrophy.

How will my doctor and I know if I have lipodystrophy?

A diagnosis of lipodystrophy is usually made by examining your body for fat changes. Your doctor may measure around your arms, thighs, waist, hips, and neck before you start medication and then periodically throughout your treatment. Abdominal **magnetic resonance imaging (MRI)** or CT scans can assess abdominal fat; however, there are currently no specific recommendations for routine assessment and monitoring of lipodystrophy.

How is lipodystrophy treated?

At this time, there are no clearly effective treatments for lipodystrophy. However, if you have lipodystrophy, you may benefit from:

- *Changes to your anti-HIV medications*—People with lipodystrophy may benefit from changes to their HIV treatment regimens. If you are taking Zerit, switching to Ziagen (abacavir, ABC) may help reduce lipodystrophy. PIs may be replaced with **non-nucleoside reverse transcriptase inhibitors (NNRTIs)**, which do not appear to cause lipodystrophy. However, the results of switching drugs are uncertain; you and your doctor may decide that changing medications is not right for you. Be sure to talk with your doctor before stopping or switching any medications.
- *Diet and exercise*—Changes to your diet and exercise regimen may help build muscle and reduce fat accumulation.
- *Medications*—If you have insulin resistance and are hyperglycemic (see **Hyperglycemia Fact Sheet**), the drug Glucophage (metformin) may help decrease abdominal fat.
- *Injections, implants, and surgery*—If you have fat wasting, you may benefit from injections of human growth hormone (hGH) to boost muscle size in your arms and legs. Injections of fat or synthetic fat substitutes like Sculptra can fill out sunken cheeks, as can cosmetic cheek implants. However, most of these treatments, along with surgery to remove fat accumulation, are still being studied and do not yet have FDA approval for the treatment of HIV-related lipodystrophy. Sculptra is the only treatment that is currently approved; it received FDA approval in August 2004.

For more information:

Contact your doctor or an *AIDSinfo* Health Information Specialist at 1–800–448–0440 or **http://aidsinfo.nih.gov**.

This information is based on the U.S. Department of Health and Human Services' *Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents* (available at **http://aidsinfo.nih.gov**).

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Osteonecrosis, Osteopenia, and Osteoporosis

What is osteonecrosis, and what are its symptoms?

Osteonecrosis means "bone death." Bone can die if its blood supply is cut off and it can't get nutrients; this is called *avascular necrosis*. Osteonecrosis occurs in the hip bones of some people with HIV, but doctors aren't sure why. It is not clear if osteonecrosis occurs because of HIV infection itself or as a side effect of the medications used to treat HIV.

Symptoms of osteonecrosis include:

- pain in the affected area of the body
- limited range of motion, joint stiffness, or limping
- muscle spasms
- progressive bone damage leading to bone collapse

How is osteonecrosis diagnosed?

If you have symptoms of osteonecrosis, early diagnosis is best made by **magnetic resonance imaging (MRI)** of the bone. MRI is able to detect osteonecrosis before bone is significantly damaged and before abnormalities can be seen on an x-ray. X-rays and CT scans may also be used to look for osteonecrotic bone damage.

What is the treatment for osteonecrosis?

While some treatments may provide relief from the pain associated with osteonecrosis, surgical removal of the dead bone and joint replacement are the only effective treatments for people who have serious osteonecrosis. If you have osteonecrosis, you may benefit from:

- *Surgery* – options range from minor outpatient procedures to reinforce bone to major surgeries such as partial or total hip replacement.

Terms Used in This Fact Sheet:

Dual energy x-ray absorptiometry (DEXA) scan: *a test that uses low energy x-rays to measure the mineral content of bones. A DEXA scan uses less radiation than a standard chest x-ray.*

Magnetic resonance imaging (MRI): *a way to take pictures of the inside of the body. MRI uses magnetic fields and radio waves instead of x-rays. MRIs are particularly useful for taking pictures of the body's soft tissues and organs.*

Protease inhibitor (PI): *class of anti-HIV medication. PIs work by blocking protease, a protein that HIV needs to make copies of itself. The PIs approved by the FDA are Agenerase, Aptivus, Crixivan, Fortovase, Invirase, Kaletra, Lexiva, Norvir, Reyataz, and Viracept.*

- *Medications* – non-steroidal anti-inflammatory drugs (NSAIDs) such as aspirin or ibuprofen may decrease the pain of osteonecrosis.
- *Assistive devices* – canes, crutches, or a walker may lesson the pain of bone disorders and may reduce the risk of falls.

What are osteopenia and osteoporosis, and what are their symptoms?

Bones are made of minerals like calcium and phosphate. *Osteopenia* is a condition in which the bones lose these minerals and become less dense. This makes the bones weaker. When bone loss becomes more severe, the condition is referred to as *osteoporosis*.

There are no obvious symptoms in the early stages of osteopenia and osteoporosis. However, fractures may occur if bone loss continues. The most common fractures involve the spine, wrists, or hips. Fractures may cause:

- neck or low back pain
- bone pain or tenderness
- loss of height
- stooped posture

This information is based on the U.S. Department of Health and Human Services' *Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents* (available at http://aidsinfo.nih.gov).

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Osteonecrosis, Osteopenia, and Osteoporosis (continued)

Who is at risk of developing osteopenia and osteoporosis?

Anyone can develop osteopenia and osteoporosis. You may be at increased risk if you take HIV **protease inhibitors (PIs)**. You may also be at increased risk if you:

- are female
- take steroids or certain other medications
- smoke
- drink excessive amounts of alcohol
- have low body weight

Anti-HIV medications can cause negative side effects that may increase your risk of osteopenia and osteoporosis. These side effects include:

- *Lipodystrophy* (also known as fat maldistribution) – a disturbance in the way the body produces, uses, and distributes fat (see **Lipodystrophy Fact Sheet**)
- *Hyperlipidemia* – high levels of cholesterol and triglycerides in the blood (see **Hyperlipidemia Fact Sheet**)

How are osteopenia and osteoporosis diagnosed?

A **dual energy x-ray absorptiometry (DEXA)** scan is used to diagnose osteopenia and osteoporosis. A DEXA scan is a painless, noninvasive procedure to determine your bone mineral density. Your bone density is then compared to people of your age and health to determine if your bones are weaker than they should be.

Although there are currently no specific guidelines for how often HIV positive people should have a DEXA scan, you should talk with your doctor about your risk factors for osteopenia and osteoporosis.

What are the treatments for osteopenia and osteoporosis?

If you have osteopenia or osteoporosis, you may benefit from:

- *Dietary supplements* – Calcium and vitamin D supplements are often recommended for people with osteopenia and osteoporosis.
- *Medications* – Bisphosphonates (Fosamax and Actonel) and raloxifene (Evista) are prescription drugs used to prevent and treat osteoporosis. Calcitonin (Miacalcin and Calcimar) and hormone replacement therapy for post-menopausal women may also be prescribed to slow bone loss and reduce the risk of fractures.
- *Assistive devices* – Canes, crutches, or a walker may lessen the pain of osteoporosis and reduce the risk of falls.

How can I prevent bone disorders from occurring?

Some things you can do to lower your risk of bone problems:

- *Consume adequate calcium and vitamin D in your diet* – High-calcium foods include low-fat milk, yogurt, and leafy green vegetables. Calcium supplements with vitamin D are another source of calcium. Adults should consume 1,000 to 1,500 mg of calcium each day.
- *Get weight-bearing exercise* – Walking, jogging, playing tennis, dancing, and other physical activities strengthen bone.
- *Don't drink excessive alcohol or smoke* – These behaviors accelerate bone loss.
- *Prevent falls* – Bone breaks or fractures increase your risk of osteonecrosis.

For more information:

Contact your doctor or an *AIDSinfo* Health Information Specialist at 1–800–448–0440 or **http://aidsinfo.nih.gov**.

This information is based on the U.S. Department of Health and Human Services' *Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents* (available at **http://aidsinfo.nih.gov**).

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Skin Rash

What kinds of skin rash can anti-HIV medications cause?

Anti-HIV medications can cause mild skin rashes as well as serious, even life-threatening rashes. The vast majority of skin rashes are mild to moderate. They usually appear within a few weeks of starting a new medication, and often go away with continued use of the medication. However, because some rashes can be serious, you should contact your doctor if you notice a skin rash. He or she will advise you about how best to manage the rash.

Which anti-HIV medications cause skin rash?

Skin rash may occur with medications from any of the three main HIV drug classes: **NNRTIs**, **NRTIs**, and **PIs**.

NNRTIs cause the majority of skin rashes, with Viramune (nevirapine) causing the most severe rashes. If you and your doctor decide to use Viramune in your HIV treatment regimen, you will likely be instructed to take only one pill a day for the first 14 days, then to increase to two pills a day. This dosing schedule may decrease your risk of developing a severe skin rash. Women appear to be at higher risk for developing Viramune-associated skin rashes than men.

NRTIs may also cause skin rashes. Ziagen (abacavir) may cause a rash that is a symptom of a severe drug hypersensitivity (allergic) reaction. If you develop a rash while taking Ziagen, notify your doctor right away. If you and your doctor decide that you need to stop taking the drug, you should never again take Ziagen; any exposure to the drug could result in an even more severe hypersensitivity reaction.

Agenerase (amprenavir) and Aptivus (tipranavir) are the PIs most likely to cause skin rash. Women taking birth control pills that contain estrogen may be more likely to develop a rash when taking Aptivus. If you are allergic to sulfa drugs, your doctor should monitor you carefully if you start taking Agenerase or Aptivus as part of your HIV treatment regimen.

Terms Used in This Fact Sheet:

Eosinophilia: *an increased number of eosinophils, a type of white blood cell. Eosinophils are a part of the body's immune system that can damage healthy tissue if they malfunction.*

Non-nucleoside reverse transcriptase inhibitor (NNRTI): *class of anti-HIV medication. NNRTIs work by blocking reverse transcriptase, a protein that HIV needs to make copies of itself. The NNRTIs approved by the FDA are Rescriptor, Sustiva, and Viramune.*

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Protease inhibitor (PI): *class of anti-HIV medication. PIs work by blocking protease, a protein that HIV needs to make copies of itself. The PIs approved by the FDA are Agenerase, Aptivus, Crixivan, Fortovase, Invirase, Kaletra, Lexiva, Norvir, Reyataz, and Viracept.*

What characterizes a severe skin rash?

Severe skin rashes cause significant damage to the skin and can result in serious complications, even death. The severe skin rashes that may occur with the use of anti-HIV medications are *Stevens-Johnson syndrome* (SJS) and *toxic epidermal necrolysis* (TEN), which are two different forms of the same kind of skin rash. TEN differs from SJS in the extent of skin damage—TEN involves at least 30% of the total body skin area. Both SJS and TEN are severe conditions that must be treated by a doctor.

This information is based on the U.S. Department of Health and Human Services' *Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents* (available at http://aidsinfo.nih.gov).

Reviewed October 2005

Skin Rash (continued)

What are the symptoms of SJS and TEN?

The symptoms of SJS and TEN include:

- flat or raised red spots on the skin that develop blisters in the center
- blisters in the mouth, eyes, genitals, or other moist areas of the body
- peeling skin that results in painful sores
- fever
- headache
- general ill feeling

Are there any other drug-associated skin rashes I should know about?

Another rare but life-threatening rash occurs as part of the *DRESS syndrome* (**d**rug **r**ash with **e**osinophilia and **s**ystemic **s**ymptoms). DRESS is characterized by a drug-related rash with **eosinophilia** and whole-body symptoms, such as fever, blood abnormalities, and organ inflammation.

How are skin rashes treated?

If you have a mild or moderate skin rash, you and your doctor may decide to change the medications in your HIV treatment regimen. Alternatively, your doctor may treat you with an antihistamine drug while you continue on the same HIV treatment regimen. Be sure to talk with your doctor before stopping or making any changes to your medications.

In cases of severe rash (SJS, TEN, or DRESS), your doctor will stop your anti-HIV medication and may admit you to the hospital. While in the hospital, you may be treated with intravenous (IV) fluids and medications such as anti-inflammatories and antibiotics. Patients with TEN and significant skin loss may need to be in a hospital's burn unit for specialized care.

If you have a severe rash while taking anti-HIV medications, you and your doctor must identify which medication caused the rash, and you should never take that medication again, even as part of a future HIV treatment regimen. Exposure to the problem medication could result in an even more severe, and perhaps fatal, drug reaction. Be aware that if you experienced a reaction to a drug in a particular class (for example, an NNRTI), you may be at risk of a serious reaction to another drug in that class. This is referred to as *cross-hypersensitivity*.

For more information:

Contact your doctor or an *AIDSinfo* Health Information Specialist at 1–800–448–0440 or **http://aidsinfo.nih.gov**.

This information is based on the U.S. Department of Health and Human Services' *Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents* (available at **http://aidsinfo.nih.gov**).

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Preclinical Study Finds Protease Inhibitor-Resistant HIV May Have Reduced Potential to Develop Resistance to Panacos' Bevirimat

WATERTOWN, Mass.--(BUSINESS WIRE)--May 29, 2007--Panacos Pharmaceuticals, Inc. (NASDAQ:PANC), a biotechnology company dedicated to developing the next generation of antiviral therapeutic products, today announced the results of a new study indicating that HIV resistant to Protease Inhibitors (PI) may have reduced potential for the development of resistance to the HIV maturation inhibitor bevirimat in laboratory assays. The study, carried out by scientists in Dr. Eric Freed's group at the HIV Drug Resistance Program at the National Cancer Institute, Frederick, MD, in collaboration with Panacos, was presented at the Cold Spring Harbor Laboratory's (CSHL) Retrovirus Conference held May 22-27, 2007 in Cold Spring Harbor, NY.

While resistance to bevirimat has not yet been reported in clinical studies, bevirimat-resistant HIV can be generated in the laboratory, as is the case with other HIV drugs. In previous studies where HIV was grown for several weeks in cell culture in the presence of bevirimat at suboptimal concentrations, mutations conferring resistance to bevirimat were found exclusively at or near bevirimat's target, the capsid-SP1 cleavage site in the HIV Gag protein. Cleavage of capsid from SP1, the final step in viral maturation, is mediated by the viral protease enzyme. Bevirimat inhibits this cleavage step by interacting with the capsid-SP1 junction in Gag, suggesting that pre-existing PI resistance mutations may have an impact on the development of bevirimat resistance.

In the new study, wild-type HIV, as well as HIV bearing major mutations conferring PI resistance, were grown in cell culture in the presence of bevirimat at suboptimal concentrations. Bevirimat resistance developed after several weeks in both wild-type and PI-resistant HIV, but took more than twice as long to develop in the PI-resistant virus. The bevirimat resistance mutation that appeared in PI-resistant virus was located at the CA-SP1 junction and has been observed previously in bevirimat resistance generation studies. The CSHL conference presentation concluded that bevirimat resistance may be less likely to arise in PI-resistant HIV strains.

Dr. Graham P. Allaway, Panacos' President and Chief Operating Officer commented, "Clinical studies to date suggest resistance to bevirimat does not develop rapidly, in contrast to some currently marketed HIV drugs, possibly because there is selective pressure to maintain the integrity of the capsid-SP1 cleavage site sequence, which is highly conserved among HIV strains. While resistance tends to develop eventually to all HIV inhibitors, the new study suggests there may be a greater hurdle to bevirimat resistance development in patients with PI-resistant virus. These patients represent one of the major groups who could potentially benefit from novel-mechanism HIV drugs such as bevirimat."

About Panacos

Panacos is developing the next generation of anti-infective products through discovery and development of small molecule oral drugs for the treatment of HIV and other major human viral diseases. HIV infects approximately 1.7 million people in North America and Western Europe and approximately 40 million people worldwide. Approximately 650,000 patients are treated annually for HIV in the United States and Western Europe. Resistance to currently available drugs is one of the most pressing problems in HIV therapy and the leading cause of treatment failure. Panacos' proprietary discovery technologies are designed to

combat resistance by focusing on novel targets in the virus life cycle, including virus maturation and virus fusion.

Panacos' lead candidate, bevirimat (PA-457), is the first in a new class of oral HIV therapeutics under development called maturation inhibitors, discovered by Panacos scientists and their academic collaborators. Based on its novel mechanism of action, bevirimat is designed to have potent activity against a broad range of HIV strains, including those that are resistant to existing classes of drugs. The Company has completed seven clinical studies of bevirimat in over 300 subjects, showing significant reductions in viral load in HIV-infected subjects and a promising safety profile, and is currently in Phase 2b clinical trials. The Company also has a second-generation program in HIV maturation inhibition in clinical testing and a research program to develop oral HIV fusion inhibitors.

Except for the historical information contained herein, statements made herein, including those relating to the clinical development of bevirimat, the potential results of treatment with bevirimat and future clinical trials and clinical practice with bevirimat are forward-looking statements made pursuant to the safe harbor provisions of the Private Securities Litigation Reform Act of 1995. These statements involve risks as set forth in the Company's filings with the Securities and Exchange Commission, including, but not limited to, the Company's Annual Report on Form 10-K for the fiscal year ended December 31, 2006 and the Company's Quarterly Report for the period ended March 31, 2007. These risks and uncertainties could cause actual results to differ materially from any forward-looking statements made herein. The Company undertakes no obligation to publicly update forward-looking statements, whether because of new information, future events or otherwise, except as required by applicable law.

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SOURCE: Panacos Pharmaceuticals, Inc.

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Panacos Announces Bevirimat Phase 2b Dose Escalation Strategy

Next Cohort to Receive 250 mg Oral Solution Dose

WATERTOWN, Mass.--(BUSINESS WIRE)--March 12, 2007--Panacos Pharmaceuticals, Inc. (NASDAQ: PANC), a biotechnology company dedicated to developing the next generation of antiviral therapeutic products, today announced that the Company and the US Food and Drug Administration (FDA) have agreed to a revised trial design for the Company's Phase 2b clinical study of bevirimat (PA-457), the first-in-class maturation inhibitor for the treatment of HIV infection. The first cohort in this study was completed in December, 2006 and confirmed the antiviral activity of bevirimat shown in previous studies and extended it to HIV patients failing therapy due to antiretroviral resistance. However, the prototype tablet formulation used in that cohort resulted in bevirimat plasma concentrations that were lower than anticipated.

The next cohorts in the Phase 2b study will test the tolerability and efficacy of bevirimat in treatment-experienced patients failing current therapy, at increasing doses using the oral liquid formulation which was utilized in the bevirimat Phase 2a trial. Phase 2b dose escalation with the liquid formulation will involve 14-day "functional monotherapy," where patients are dosed with either placebo or bevirimat in combination with their failing antiretroviral therapy. This is similar to the first Phase 2b cohort, except that patients will not continue on to extended dosing. The primary endpoints of the trial will be safety and viral load reduction on day 15. To expedite dose escalation, the cohort size will be reduced to eight patients on bevirimat and two on placebo, from 12 on bevirimat and four on placebo in the first cohort in the study. Dosing of the next cohort will be initiated at 250 mg of the oral solution once daily, a higher dose than previously studied in multiple-dose trials of bevirimat solution. Panacos plans to escalate the dose in subsequent cohorts by 50 mg per cohort following review of the safety and antiviral response from each preceding cohort. The Company plans to release data from each cohort as analysis is completed.

"We are very pleased to continue dose escalation in our Phase 2b clinical trial," said Alan W. Dunton, M.D., Panacos' Chief Executive Officer. "While we saw several patients with antiviral responses in the first Phase 2b cohort, we believe that the 250 mg liquid dose cohort should provide substantially greater bevirimat plasma concentrations with the potential for correspondingly greater antiviral responses. Models relating antiviral response to drug levels based on earlier bevirimat clinical data indicated that doses of the liquid solution in the 300-400 mg range would be likely to approach the maximum antiviral effect. Our new study design should allow us to see antiviral response data from that dose range later this year."

After dose escalation to determine the optimal dose(s) of bevirimat, the Company plans to dose one or more cohorts for at least a three-month period, using an optimized formulation suitable for pivotal clinical trials. These long-term dosing cohorts may enroll greater numbers of patients in need of new treatment options, and the Company believes they would be the basis for demonstrating safety and efficacy prior to initiating pivotal clinical trials of bevirimat.

Dr. Dunton commented, "We continue to make progress on development of a formulation suitable for extended dosing in Phase 2b and look forward to providing further updates on that program over the next few months. Our goal is to develop an optimized formulation for

extended dosing in Phase 2b later this year. Based on this progress and the dose escalation plan, we believe we will be able to initiate pivotal trials of bevirimat in 2008."

About Panacos

Panacos is developing the next generation of anti-infective products through discovery and development of small molecule oral drugs for the treatment of HIV and other major human viral diseases. HIV infects approximately 1.7 million people in North America and Western Europe and approximately 40 million people worldwide. Approximately 650,000 patients are treated annually for HIV in the United States and Western Europe. Resistance to currently available drugs is one of the most pressing problems in HIV therapy and the leading cause of treatment failure. Panacos' proprietary discovery technologies are designed to combat resistance by focusing on novel targets in the virus life cycle, including virus maturation and virus fusion.

Panacos' lead candidate, bevirimat (PA-457), is the first in a new class of oral HIV therapeutics under development called maturation inhibitors, discovered by Panacos scientists and their academic collaborators. Based on its novel mechanism of action, bevirimat is designed to have potent activity against a broad range of HIV strains, including those that are resistant to existing classes of drugs. The Company has completed seven clinical studies of bevirimat in over 300 subjects, showing significant reductions in viral load in HIV-infected subjects and a promising safety profile, and is currently in Phase 2b clinical trials. The Company also has a second-generation program in HIV maturation inhibition in Phase 1 clinical testing and a research program to develop oral HIV fusion inhibitors.

Except for the historical information contained herein, statements made herein, including those relating to the clinical development of bevirimat and the Company's second-generation program in HIV maturation inhibition and HIV fusion inhibitors, including the timing thereof, the potential results of treatment with bevirimat and future clinical trials and clinical practice are forward-looking statements made pursuant to the safe harbor provisions of the Private Securities Litigation Reform Act of 1995. These statements involve risks as set forth in the Company's filings with the Securities and Exchange Commission, including, but not limited to, the Company's Annual Report on Form 10-K for the fiscal year ended December 31, 2005, and subsequent reports on Form 10-Q. These risks and uncertainties could cause actual results to differ materially from any forward-looking statements made herein. The Company undertakes no obligation to publicly update forward-looking statements, whether because of new information, future events or otherwise, except as required by applicable law.

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Panacos Begins Phase 1 Clinical Study of Second Generation Maturation Inhibitor PA-040

WATERTOWN, Mass.--(BUSINESS WIRE)--Feb. 27, 2007--Panacos Pharmaceuticals, Inc. (Nasdaq:PANC), a biotechnology company dedicated to developing the next generation of antiviral therapeutic products, today announced that it has initiated a Phase 1 clinical trial of PA-1050040 (also referred to as "PA-040"), an investigational maturation inhibitor for the treatment of HIV.

This Phase 1 study is designed to evaluate the safety and pharmacokinetic properties of PA-040 in humans after a single dose. Maturation inhibition is a new target discovered by Panacos scientists and their academic collaborators. The first-in-class HIV maturation inhibitor, bevirimat (PA-457), has shown significant anti-HIV activity in HIV patients and is in Phase 2b clinical testing. The Company's second-generation maturation inhibitor program is designed to develop chemical analogs of bevirimat with distinct pharmacological properties including the potential to have activity against HIV strains resistant to bevirimat, should these resistant strains appear in the clinic in the future.

In vitro studies with PA-040 have shown that the compound has a lower level of binding to human serum proteins than bevirimat, which may result in greater levels of free drug in patients dosed with the compound, and thus the potential ability to have activity against HIV strains that exhibit partial bevirimat resistance. Furthermore, PA-040 retains wild-type activity against one of two bevirimat-resistant HIV isolates that represent the most-frequently mutated amino acids found by in vitro resistance-selection experiments performed to date.

"The initiation of clinical testing with our second maturation inhibitor is a major milestone for Panacos as we build our maturation inhibitor franchise," said Graham Allaway, Ph.D., Panacos' President and Chief Operating Officer. "Having already demonstrated proof of concept of maturation inhibition with bevirimat, we plan to test several second generation compounds, including PA-040, in single dose testing and then select the optimum compound to take into multiple dose human studies."

About Panacos

Panacos is developing the next generation of anti-infective products through discovery and development of small molecule oral drugs for the treatment of HIV and other major human viral diseases. HIV infects approximately 1.7 million people in North America and Western Europe and approximately 40 million people worldwide. Approximately 650,000 patients are treated annually for HIV in the United States and Western Europe. Resistance to currently available drugs is one of the most pressing problems in HIV therapy and the leading cause of treatment failure. Panacos' proprietary discovery technologies are designed to combat resistance by focusing on novel targets in the virus life cycle, including virus maturation and virus fusion.

Panacos' lead candidate, bevirimat (PA-457), is the first in a new class of oral HIV therapeutics under development called maturation inhibitors, discovered by Panacos scientists and their academic collaborators. Based on its novel mechanism of action, bevirimat is designed to have potent activity against a broad range of HIV strains, including those that are resistant to existing classes of drugs. The Company has completed seven clinical studies of bevirimat in over 300 subjects, showing significant reductions in viral load in HIV-infected subjects and a

promising safety profile, and is currently in Phase 2b clinical trials. The Company also has a second-generation program in maturation inhibition in clinical testing and a research program to develop oral fusion inhibitors.

Except for the historical information contained herein, statements made herein, including those relating to the clinical development of bevirimat and PA-040, or the development of other maturation inhibitors or oral fusion inhibitors, the potential results of treatment with bevirimat or other maturation inhibitors, future clinical trials and clinical practice are forward-looking statements made pursuant to the safe harbor provisions of the Private Securities Litigation Reform Act of 1995. These statements involve risks as set forth in the Company's filings with the Securities and Exchange Commission, including, but not limited to, the Company's Annual Report on Form 10-K for the fiscal year ended December 31, 2005, and subsequent reports on Form 10-Q. These risks and uncertainties could cause actual results to differ materially from any forward-looking statements made herein. The Company undertakes no obligation to publicly update forward-looking statements, whether because of new information, future events or otherwise, except as required by applicable law.

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Panacos Announces Substantial Antiviral Response in Bevirimat 250 mg Cohort, Data Support Further Dose Escalation in Phase 2b Study

Company to Hold a Conference Call at 5:00 p.m. EDT Today

WATERTOWN, Mass.--(BUSINESS WIRE)--June 20, 2007--Panacos Pharmaceuticals, Inc. (NASDAQ: PANC), a biotechnology company dedicated to developing the next generation of antiviral therapeutic products, today announced preliminary results from the 250 mg cohort of a Phase 2b study of bevirimat (PA-457) in patients failing HIV therapy due to drug resistance. Bevirimat plasma concentrations and antiviral effect were approximately double those seen in the first Phase 2b cohort that had used a suboptimal tablet formulation. No safety or tolerability issues with bevirimat arose in this cohort, consistent with previous clinical experience. The results of the 250 mg cohort support further dose escalation as planned in order to fully explore the dose-response relationship of bevirimat.

Following dosing with 250 mg of bevirimat solution administered on top of patients' failing background regimens, the mean trough plasma concentration of bevirimat at steady state was 38.3 micrograms/ml compared to 19.9 micrograms/ml at steady state in the 400 mg tablet cohort. These plasma concentrations were also higher than the steady state concentration of 33.8 micrograms/ml seen in the top dose of the earlier Phase 2a monotherapy study, and were in line with expectations based on previous clinical studies of the oral solution formulation.

A mean viral load reduction of 0.68 log10 was seen in bevirimat treated patients on day 15, the primary endpoint of the study. This compared to placebo patients who had a mean increase in viral load of 0.18 log10 and to bevirimat patients in the 400 mg tablet cohort, who had a mean reduction in viral load of 0.36 log10. At the 250 mg dose, 71% of patients had a confirmed viral load reduction of at least 0.50 log10 during the course of the study. The antiviral effect in the 250 mg cohort was comparable to the 200 mg cohort in the Phase 2a study at day 11, the primary endpoint of the Phase 2a study. The mean viral load reduction in the 250 mg cohort in the current study of highly treatment-experienced patients was 0.79 log10, compared to 0.90 log10 in the 200 mg cohort in the Phase 2a study of mostly treatment-naive patients.

"We were pleased to have these data supporting bevirimat's efficacy in patients failing therapy due to resistance - the initial target population for our first planned NDA submission," said Alan W. Dunton, M.D., Panacos' Chief Executive Officer. "This confirms our belief that the lower than expected plasma concentrations observed in the earlier 400 mg tablet cohort were caused by the prototype tablet formulation, and not by bevirimat itself. In the 250 mg cohort, we saw potent antiviral activity that was consistent with bevirimat plasma levels, which supports going to higher doses to achieve greater responses. We anticipate completing a 300 mg dose cohort in the third quarter, continuing to escalate towards the peak of the dose-response curve thereafter."

About the Phase 2b Bevirimat Study

The objectives of the Phase 2b study of bevirimat are to examine the antiviral efficacy, pharmacokinetics, and safety of bevirimat in combination with other HIV drugs. The first cohort in this study, which used a tablet dose of 400 mg, was completed in December 2006. The

results of this cohort confirmed the antiviral activity of bevirimat shown in previous studies and extended it to HIV patients failing therapy due to antiretroviral resistance. However, the prototype tablet formulation used in that cohort resulted in bevirimat plasma concentrations that were lower than anticipated.

A revised Phase 2b trial design was announced in March 2007. The new design tests the tolerability and efficacy of bevirimat in treatment-experienced patients failing current therapy at increasing doses using the oral liquid formulation which was utilized in the bevirimat Phase 2a trial. Phase 2b dose escalation with the liquid formulation involves 14-day "functional monotherapy," where patients are dosed with either placebo or bevirimat in combination with their failing antiretroviral therapy. This design is similar to the first Phase 2b cohort, except that patients do not continue on to extended dosing, which was a feature of the tablet cohort. The primary endpoints of the trial are safety, pharmacokinetics, and viral load reduction on day 15. Panacos plans to continue escalating the dose in subsequent cohorts by 50 mg per cohort following a review by the Company, FDA, and outside clinical experts of the safety and antiviral response from each preceding cohort, releasing data from each cohort as analysis is completed.

Conference Call

The Company will host a conference call to discuss these results at 5:00 p.m. today (EDT). The conference call can be accessed via the web at www.panacos.com or by dialing (866) 383-8003 (domestic) or (617) 597-5330 (international), between 4:45 and 4:55 p.m. and entering the passcode 24132480. A replay of the conference call will be available from 7:00 p.m. on June 20, 2007 until Friday, July 20, 2007, and can be accessed via the web at www.panacos.com or by dialing toll-free (888) 286-8010, and outside the U.S. (617) 801-6888 with passcode 29638058.

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Except for the historical information contained herein, statements made herein, including those relating to bevirimat's clinical development, the potential results of treatment with bevirimat and future clinical trials

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